II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 54-83 were pending at the time of the Office Action. No claims have been amended herein. No claims have been canceled. New claim 84 has been added. Written description support for claim 84 is discussed in the specification below. Therefore, claims 54-84 are now pending and presented for reconsideration.

B. The Provisional Rejections Under the Judicially Created Doctrine of Obviousness-type Double Patenting

The Examiner has set forth provisional rejections of four subsets of claims under the judicially created doctrine of obviousness-type double patenting based on copending Applications No. 10/732,919, 09/599,152, 10/672,763, and 10/703,405. Without conceding that the claims at issue are obvious in view of the cited claims in these applications, Applicants agree to seriously consider filing a terminal disclaimer if the Examiner indicates that there is reasonable allowable subject matter. The Examiner is invited to contact Applicants' representative to discuss this matter further if necessary.

C. The Rejections Under 35 U.S.C. §103(a) have been Overcome

Claims 54-68, 70, and 80 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Dean *et al.* (U.S. Patent 5,716,596). According to the Examiner, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Dean *et al.* and generate a method of delivering a radionuclide using labeled bis-aminoethane thiol (BAT) targeting ligand conjugates since Dean *et al.* is said to disclose use of BAT targeting ligand conjugates which may be administered to humans for diagnostic and therapeutic purposes. Applicants respectfully traverse.

In rejecting claims under 35 U.S.C. §103, the Examiner bears the initial burden of presenting a *prima facie* case of obviousness. See *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). In order to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) the prior art reference (or references when combined) must teach or suggest all the claim limitations; (2) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (3) there must be a reasonable expectation of success. *Manual of Patent Examining Procedure* § 2142. See also *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed Cir. 1991) (emphasizing that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must be both found in the prior art, and not based on applicant's disclosure). It is important to note that all three elements must be shown to establish a *prima facie* case of obviousness. Thus, if one element is missing, a *prima facie* case of obviousness does not exist.

1. Dean *et al.* Fails to Teach or Suggest Conjugates Capable of Being Taken Up Into Target Cells

The Examiner has failed to establish a *prima facie* case of obviousness because she has failed to identify any teaching or suggestion in Dean *et al.* that addresses any conjugate being taken up into a target cell. Dean *et al.* is a patent that pertains to certain radioactively labeled somatostatin-derived peptides for imaging and therapeutic use. Dean *et al.* teaches that:

> "Somatostatin exerts its effects by binding to specific receptors expressed at the cell surface of cells comprising the central nervous system, the hypothalamus, the pancreas, and the gastrointestinal tract. These high-affinity somatostatin binding sites have been found to be abundantly expressed at the cell surface of most endocrine-active tumors arising from these tissues. Expression of high-affinity binding sites for somatostatin is a marker for these tumor cells, and specific

binding with somatostatin can be exploited to locate and identify tumor cells *in vivo*."
Dean *et al.*, col. 2, lines 1-9.

Further, Dean *et al.* teaches that:

"Radiotherapeutic embodiments ... are useful in the treatment of somatostatin-related diseases or other ailments in animals, preferably humans, including but not limited to cancer and other diseases characterized by the growth of malignant or benign tumors capable of binding somatostatin or somatostatin analogues **via the expression of somatostatin receptors on the cell surface of cells comprising such tumors**." Dean *et al.*, col. 7, lines 33-42. (emphasis added).

Thus, Dean *et al.* teaches that its conjugates allegedly target cells by binding to cell surface receptors, and not entering into target cells. The Examiner has failed to identify, nor do Applicants identify, any teaching or suggestion in Dean *et al.* that its conjugates have the capability of being taken up into target cells.

The conjugates set forth in Dean *et al.* are distinct from the conjugates set forth in the present invention. The conjugates set forth in Dean *et al.* require the presence of a peptide conjugate, resulting in conjugates that are quite large and bulky. It is unclear whether these conjugates, in view of their size, would even be capable of uptake into a cell.

Further, the radionuclide is covalently linked to the peptide in the conjugates set forth in Dean *et al.* In contrast, in the present invention, the radionuclide is covalently linked to the bis-aminoethanethiol moiety.

There is simply no basis in Dean *et al.* for one of ordinary skill in the art to conclude that the conjugates set forth in Dean *et al.* are capable of being taken up into target cells. Nor is this limitation inherent, or necessarily required. As set forth above, Dean *et al.* makes it clear that it is the binding to the cell surface of target cells that is beneficial, with no mention of any requirement for uptake into the cells.

Therefore, because the Examiner has failed to set forth a teaching or suggestion as to each and every limitation of the claimed invention, there can be no *prima facie* case of obviousness.

2. Dean *et al.* Does Not Teach or Suggest Radionuclide-Labeled Ethylenedicysteine-Targeting Ligand Conjugates

Further, Dean *et al.* does not teach or suggest radionuclide-labeled ethylenedicysteine targeting ligand conjugates, as recited in claims 61-62. The Examiner has filed to identify any teaching or suggestion in Dean *et al.* pertaining to ethylenedicysteine, or any targeting ligand conjugate comprising ethylenedicysteine. Nor do Applicants identify any such teaching or suggestion. Therefore, as to these claims, there is an additional basis for no *prima facie* case of obviousness.

3. New Claim 84

a. The Specification Provides Written Description Support for New Claim 84

New claim 84 differs from existing claim 54 in that new claim 84 recites "radionuclide-labeled bis-aminoethanethiol (BAT) dicarboxylic acid –targeting ligand conjugate" instead of "radionuclide-labeled bis-aminoethanethiol (BAT)–targeting ligand conjugate. Written description support for radionuclide-labeled bis-aminoethanethiol (BAT) dicarboxylic acid – targeting ligand conjugate" can be generally found throughout the specification. Exemplary written description support can be found in FIG. 1, which depicts the chemical structure of ethylenedicysteine (EC), a bis-aminoethanethiol dicarboxylic acid. ^{99m}Tc-EC-folate, depicted in FIG. 1, is a "radionuclide-labeled bis-aminoethanethiol (BAT) dicarboxylic acid –targeting ligand conjugate." Folate is conjugated to one of the carboxylic acid moieties of EC. Further, FIG. 2 depicts conjugation of EC with methotrexate to form ^{99m}TcO-EC-MTX, another

radionuclide-labeled bis-aminoethanethiol (BAT) dicarboxylic acid –targeting ligand conjugate. Other synthetic schemes depicting conjugation of EC to other targeting ligands are shown in FIG. 3 (^{99m}TcO-EC-Tomudex), FIG. 7 (^{99m}Tc-EC-Metronidazole), FIG. 8A (^{99m}Tc-EC-nitroimidazole), FIG. 21 (^{99m}Tc-EC-colchicine), FIG. 36 (^{99m}Tc-EC-neomycin), FIG. 49 (^{99m}Tc-EC-glucosamine), and FIG. 54 (^{99m}Tc-EC-GAP-glucosamine).

The Federal Circuit has stated that the test for the written description requirement is whether the application relied upon "reasonably conveys" to the artisan that the inventor had possession of the claimed subject matter. *In re Daniels*, 144 F.3d 1452, 1456, 46 USPQ2d 1788, 1790 (Fed. Cir. 1998). See also *Markman v. Westview Instruments, Inc.* 52 F.3d 967, 34 USPQ 2d 1321 (Fed. Cir. 1995) (en banc) ("Claims must be read in view of the specification, of which they are a part.").

Written description for remaining limitations of the new claims can also be generally found throughout the specification, such as in the claims as originally filed.

In view of the above, one of ordinary skill in the art would understand that the specification reasonably conveys to one of ordinary skill in the art that the inventors had possession of claims directed to methods of delivering radionuclides into target cells of a subject using radionuclide-labeled bis-aminoethanethiol (BAT) dicarboxylic acid –targeting ligand conjugates."

b. Dean *et al.* Fails to Teach or Suggest Radionuclide-Labeled Bis-Aminoethanethiol (BAT) Dicarboxylic acid-Targeting Ligand Conjugates

As set forth above, in order to establish a *prima facie* case of obviousness, it is the Examiner's burden to establish that the cited prior art references teaches or suggests each limitation of the claimed invention. Applicants have reviewed Dean *et al.* and find no teaching or suggestion in Dean *et al.* pertaining to radionuclide-labeled bis-aminoethanethiol (BAT)

dicarboxylic acid targeting ligand conjugates. Applicants invite the Examiner to point out any such teaching or suggestion in Dean *et al.*

Furthermore, for the reasons set forth above, there is no *prima facie* case of obviousness because the Examiner has not demonstrated that Dean *et al.* teaches or suggests the limitation "wherein the conjugate is capable of being taken up into the target cells." Therefore, there is no *prima facie* case of obviousness as to the new claims.

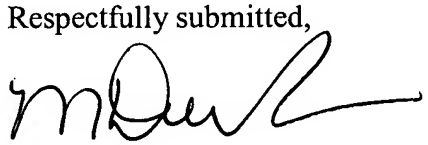
4. Conclusion

In view of the above, the Examiner has failed to establish a *prima facie* case of obviousness as to any of the claims based on Dean *et al.* Therefore, it is respectfully requested that the rejection of claims 54-68, 70, and 80 should be withdrawn.

D. Conclusion

It is submitted that in light of the foregoing, the invention embraced by the pending claims has been shown to be patentable, and favorable reconsideration is earnestly solicited. The Examiner is invited to contact the undersigned attorney at (512) 536-5639 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



Monica A. De La Paz
Reg. No. 54,662
Attorney for Applicants

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
(512) 474-5201

Date: November 23, 2005